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Indium-mediated formation of propargyl ketones from aldehydes or acyl chlorides

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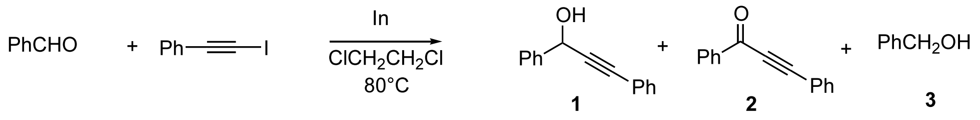
Abstract—Propargyl ketones were prepared from aldehydes via an indium-mediated alkynylation reaction followed by an indium-mediated Oppenauer oxidation. They were also obtained via an indium-mediated alkynylation of the relevant acyl chlorides. © 2003 Elsevier Science Ltd. All rights reserved.

Barbier-type indium-mediated reactions have become popular in the alkylation of carbonyl compounds with allylic bromides or iodides, especially in water media.[1] The reaction was applied to propargylic and α-carbonyl halides.[1] Recently we reported that alkynyl iodides could be reduced by indium to react with aldehydes and ketones to produce propargylic alcohols in good yields.[2] Propargyl ketones were observed as by-products in the alkynylation of aldehydes; we suggested that an Oppenauer-type oxidation of the indium(III) alkoxide intermediate was responsible for this behaviour.[2] This oxidation step might be formally explained by a β-elimination reaction and therefore might be facilitated by heating. Thus we chose to perform the reaction at 80°C at the reflux of dichloroethane rather than at 40°C at the reflux of dichloromethane as previously described for the formation of propargyl alcohols.[2]

We first studied the indium-mediated alkynylation of benzaldehyde with phenylalkynyl iodide in dichloroethane at 80°C (Scheme 1). In these conditions the benzylic alcohol **3** was observed along with the alkynyl ketone **2**. The small excess of **3** compared to **2** could arise from a direct reduction of benzaldehyde. The stoichiometric ratio between benzaldehyde and phenylalkynyl iodide is equal to 2; a small excess of benzaldehyde with respect to this stoichiometric ratio gave the best results (Table 1).

In a typical experiment, indium powder (172 mg, 1.5 mmol) was placed in a Schlenk tube under argon, followed by the addition of dichloroethane (6 mL) and phenylalkynyl iodide (228 mg, 1 mmol) and then benzaldehyde (244 mg, 2.3 mmol). The heterogeneous mixture was stirred at reflux during 6 h. The reaction was quenched by addition of a sodium bicarbonate aqueous solution. The product was extracted with ether, washed with brine, dried with anhydrous $MgSO_4$, concentrated under reduced pressure, and separated with silica gel chromatography using a mixture of cyclohexane and ethyl acetate as the eluent, affording 1,3-diphenylpropynone in 86% yield.

The reaction was tested with various aldehydes (Scheme 2) under the same conditions and with another alkynyl iodide (Table 2). The yields were good for aromatic or hindered aldehydes (Table 2, runs 1–4, 6, 8–9); for straight aldehydes and for aldehydes with an α-acidic proton (Table 2, runs 5 and 7) the alkynylation step occurred but the following Oppenauer oxidation failed. This was probably due to an aldol condensation since



Scheme 1.

Keywords: indium; propargyl ketone; alkynylation; Barbier reaction; Oppenauer oxidation.

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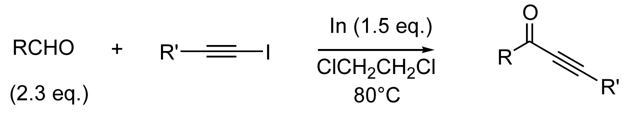
Table 1. Indium-mediated alkynylation of phenylalkynyl iodide with benzaldehyde

PhCHO (equiv.)	In (equiv.)	Time (h)	Yield of **2** (%)	Ratio **2**/**1**	Ratio **2**/**3**
1.2	1.2	7	41	67/33	45/55
2.2	1.2	9	73	83/17	37/63
3	1.2	9	77	90/10	47/53
2.3	1.5	6	86	99/1	47/53



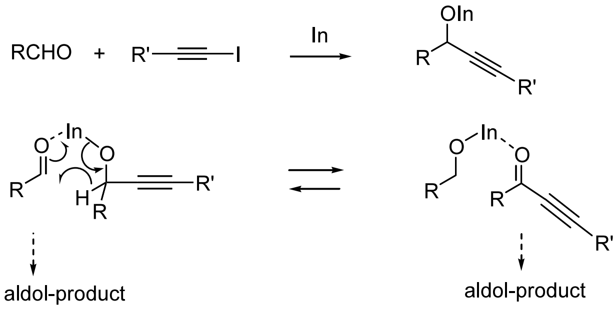
Scheme 2.

Table 2. Indium-mediated preparation of propargyl ketones from aldehydes

Run	Aldehyde R	Alkynyl iodide R′	Time (h)	Yield (%)
1	Ph	Ph	6	86
2	$CF_3C_6H_4$	Ph	3	83
3	$CH_3C_6H_4$	Ph	4.5	62
4	Anthracenyl	Ph	6	61
5	$CH_3(CH_2)_6$	Ph	8	–
6	C_6H_{11}	Ph	8	84
7	$PhCH(CH_3)$	Ph	9	–
8	$(CH_3)_3$	Ph	5	93
9	Ph	*n*-Bu	6	70

such a side-reaction has been frequently observed during Oppenauer oxidation.[3]

The mechanism of the reaction of propargyl ketone formation lies on the indium secondary alkoxide transient formation during the alkynylation step (Scheme 3). This secondary alkoxide is easily oxidable giving rise to a propargylic ketone which cannot react with a second propargylic indium species as an unsaturated ketone.[2] Side-reactions might be the aldolisation of the enolisable propargylic ketones or aldehydes (Scheme 3). A similar mechanism was recently described to explain the formation of allyl ketones via Hiyama–Nozaki reactions followed by a chromium-mediated Oppenauer oxidation but the tandem reaction was limited to aromatic aldehydes, which are not enolisable.[4]



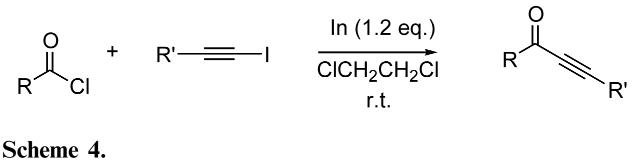
Scheme 3.

Since linear aliphatic aldehydes failed to lead to the corresponding propargyl ketones, we investigated the straightforward alkynylation of acyl chlorides mediated by indium (Scheme 4). Acyl chlorides were formerly used as electrophiles in indium-mediated allylation leading to homoallylic ketones in good yields.[5]

Thus, in a typical experiment indium powder (138 mg, 1.2 mmol) was placed in a Schlenk tube under argon, followed by the addition of dichloromethane (6 mL), phenylalkynyl iodide (228 mg, 1 mmol) and then decanoyl chloride (210 mg, 1.1 mmol). The uncoloured mixture became dark red within 2 min and was stirred at room temperature during 1 h. The reaction was quenched by addition of a sodium bicarbonate aqueous solution. The product was extracted with ether, washed with brine, dried with anhydrous $MgSO_4$, concentrated under reduced pressure, and separated with silica gel chromatography using a mixture of cyclohexane and ethyl acetate as the eluent, affording 205 mg of 1-phenyldodec-1-yn-3-one (80% yield).

The reaction was applied to various acyl chlorides giving rise to the corresponding propargyl ketones in good yields (Table 3).

In summary, aromatic and hindered aldehydes were easily transformed into propargyl ketones by an indium-mediated alkynylation followed by an indium-mediated Oppenauer oxidation. Propargylic ketones could also be obtained by a straightforward alkynylation of acyl chlorides mediated by indium. All the reactions were performed in chlorinated solvents which are rather unusual in Barbier-type reactions. These



Scheme 4.

Table 3. Indium-mediated preparation of propargyl ketones from acyl chlorides

R	R′	Time (h)	Yield (%)
C_9H_{18}	Ph	1	80
C_7H_{15}	Ph	1	78
$(CH_3)_3C$	Ph	1	82
CH_3	Ph	0.5	54
Ph	Ph	3.5	50
ClC_6H_4	Ph	1	73
$(CH_3)_3C$	*n*-Bu	2.5	55

non-coordinating solvents allowed us to increase the reactivity of the organoindium species involved in the process.

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